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**TITLE:**

Effect of a Hypocretin/Orexin Antagonist on Neurocognitive  
Performance

**PRINCIPAL INVESTIGATOR:**

Dr. Thomas Neylan

**CONTRACTING ORGANIZATION:**

Northern California Institute for Research and Education  
4150 Clement St. (116P)  
San Francisco, CA 94109

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14. ABSTRACT  During Year 4, revisions were made to the protocol which allowed female participants to be dosed within either phase of the menstrual cycle so long as they do not meet criteria for Premenstrual Dysphoric Disorder and/or moderate to severe Premenstrual Syndrome. Likewise, modifications to recruitment materials and compensation schedules have increased enrollment and retention. Safety reports continue to be sent to Actelion on a monthly basis. Both blinded and unblinded monitoring visits of study procedures and facilities are ongoing. Throughout Year 4, many new study team members were hired and trained (Study Coordinator, Recruiter, and Research Assistant). The study team also expanded to include additional informed consent administrators, clinical interviewers, as well as sleep technicians and neuropsychological assessment administrators in order to reach the our quarterly enrollment goals. Enrollment is expected to increase due to the actions taken above.		

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## Table of Contents

	<u>Page</u>
Introduction.....	1
Body.....	1
Key Research Accomplishments.....	5
Reportable Outcomes.....	6
Conclusion.....	6
Description of Appendices.....	6

**ANNUAL PROGRESS REPORT**  
**September 30, 2013 (Revised December 18, 2013)**

Effect of a Hypocretin/Orexin Antagonist on Neurocognitive Performance  
USAMRMC Grant W81XWH-09-2-0080  
Thomas Neylan, M.D., Principal Investigator

**INTRODUCTION**

An integrated translational study will be conducted to examine the effect of a novel hypocretin/orexin antagonist, almorexant (ALM), compared to a standard hypnotic, zolpidem (ZOL), and placebo (PBO) on neurocognitive performance at peak concentration post dosing. The human study component (Task 1; responsible individual: Thomas Neylan, M.D.) will establish whether ALM is superior to ZOL in relation to neurocognitive side effects. It is hypothesized that healthy human subjects receiving 10mg of zolpidem will show greater impairment in neurocognitive performance compared to subjects receiving 100mg or 200mg doses of almorexant or placebo. Study subjects (n=200) will receive a randomly assigned, one-time dose of the study drug in an inpatient hospital setting. A battery of neurocognitive, objective alertness, and subjective symptom assessments will be administered prior to and following dosing. Assessments to be administered were selected based upon their demonstrated sensitivity to sleep-inducing agents and their military relevance. The animal study component (Tasks 2 – 5; responsible individual: Thomas Kilduff, Ph.D.) will compare the neural circuitry that underlies the activity of the abovementioned compounds, their effects on sleep and performance, and the effects of these compounds on biomarkers associated with normal sleep.

**BODY**

Progress associated with each task outlined in the approved Statement of Work is listed below:

***Task 1:*** *Test the hypothesis that healthy human subjects receiving ZOL 10mg will show greater impairment in neurocognitive performance compared to subjects receiving PBO or the 2 doses (100mg, 200mg) of ALM.*

The Task 1 subtasks listed below have been completed prior to or during Year 4:

**Subtask #1: Write Protocol**

The study protocol was finalized during Year 1, and modifications were made to the protocol during Year 2, Year 3 and Year 4. The current version of the protocol is included in Appendix 1.

**Subtask #2: Obtain Scientific and Human Use Approvals**

Study documentation was submitted to the appropriate Institutional Review Boards (IRBs) and the Food and Drug Administration (FDA) for approval prior to the end of Year 1. All human subjects approvals were obtained during Year 2. Approval timelines are detailed below:

- IRB Approval:

#### **Initial Approval**

The University of California, San Francisco Committee on Human Research (UCSF CHR) provided initial approval on October 29, 2010. The Department of Veterans Affairs Medical Center Research and Development Committee (VA R&D Committee) provided approval on January 6, 2011. The U.S. Army Medical Research and Materiel Command Human Research Protection Office (USAMRMC HRPO) provided initial approval on March 9, 2011.

#### **Approval of Amendments**

An amended Investigator's Brochure was provided by Actelion Pharmaceuticals on March 23, 2011 which necessitated revisions to the study protocol and informed consent document. Enrollment could not begin until all Institutional Review Boards approved the revised study documents. The UCSF CHR and the VA R&D Committee approved the revisions on May 3, 2011. The USAMRMC HRPO approved the revisions on May 10, 2011, at which point enrollment could be initiated. Informed consent and VA HIPAA documents were revised and approved by UCSF CHR on February 7, 2012 (modifications included giving participants the option to consent to be contacted for participation in other research studies within the Stress & Health Research Program, as well as requesting that participants continue filling out a sleep diary and wearing an actigraph during the hospital portion of the study). The informed consent was again revised and approved by UCSF CHR on October 9<sup>th</sup>, 2013 and on January 15<sup>th</sup>, 2013 (modifications included providing participants with additional information related to FDA changes to the recommended dose of Zolpidem for women, allowing female participants to be dosed during either the follicular or luteal phase of menstruation, adding a VA consent form for use of picture and/or voice, compensation allocation changes, and updates to recruitment text).

#### **Continuing Review**

An annual continuing review application was approved by the UCSF CHR on September 3, 2013, extending the study's approval expiration to September 2, 2014. Continuing review approval from the VA R&D Committee was received on September 17, 2013. All continuing review approvals were last submitted to a continuing review analyst at the USAMRMC HRPO on September 27, 2012 and will be submitted again as requested.

- Investigational New Drug Application (IND): At the conclusion of Year 1, an IND application was filed with the FDA in order to obtain approval to receive study drug from Actelion Pharmaceuticals. The IND went into effect on October 21, 2010. The study protocol was re-submitted to the FDA on May 18, 2011 following revisions in response to the Investigator's Brochure Amendment received from Actelion Pharmaceuticals in March, 2011. In accordance with FDA requirements, an annual progress report was submitted on January 12<sup>th</sup>, 2012 and the next report will be submitted by no later than December 20<sup>th</sup>, 2013.

### **Subtask #3: Purchase Study Related Equipment/Supplies**

The majority of study related equipment (including sleep equipment, actigraphs, psychomotor vigilance tests, and neuropsychological testing supplies) was purchased and tested during Year 1. Further testing and piloting of the equipment was performed during the early part of Year 2. All remaining study supplies (including drug testing kits and additional sleep equipment) were purchased and tested during Year 2.

The study drug (provided by Actelion Pharmaceuticals) arrived onsite at the UCSF Medical Center pharmacy in March, 2011. An external unblinded monitor has been appointed to perform regular drug accountability checks to confirm that drug is stored properly and in accordance with expiration dates. The most recent monitoring visit took place on April 30, 2013.

Clinical Trial Management Software was purchased during Year 3, and we began using this software in September of 2013 to manage recruitment. Likewise, PRANA sleep software was purchased in 2013.

### **Subtask #4: Train Laboratory Personnel**

Key study personnel were hired and trained during Year 1, Year 2 and Year 3. In Y4, the study coordinator, recruiter and research assistant left the team. New team members were hired and trained shortly thereafter and we expect productivity to increase as we move into Y5.

### **Subtask #5: Collect Data on 200 Volunteers**

Recruitment and enrollment efforts were initiated in May 2011 (Y2, Q3), following receipt of all regulatory approvals. Enrollment details and future plans are outlined below:

#### **A.) Enrollment Progress During Year 4**

Summary of Y4 Enrollment Progress	
Total Number of Responses to Advertising in Y4	1020
Total Number of Participants who Completed Phone Screening Procedures in Y4	933
Total Number of Participants who Consented in Y4	177
Total Number Deemed Eligible in Y4	81
Total Number Enrolled in study and dosed with Study Medication in Y4	73

Table 1. Summary of Year 4 Enrollment Progress

- **Advertising:** Advertising efforts have involved monthly postings on the internet. These ads have generated a substantial response rate, as approximately 1020 individuals have shown an interest in the study throughout the past year (100 more than last year). Throughout Year 4, 933 interested participants were screened by phone prior to being scheduled for full eligibility assessments.
- **Screening:** From 9/1/2012 to 8/31/13, 177 participants met phone screen requirements, provided informed consent, and were invited to take part in full screening procedures at the San Francisco VA Medical Center. Screening procedures include a mental health screening, self-report questionnaires related to caffeine use, tobacco use, alcohol use, and

sleep habits, a physical exam, urine drug and pregnancy screens, and a blood draw for hematology and serum chemistry panels.

- **Eligible Participants:** From 9/1/2012 to 8/31/13, 81 participants were identified as eligible. 73 completed their inpatient hospital stay and dosing procedures. As of the end of Y4, a total of 118 participants have enrolled in the study and have been dosed with the study drug.

B.) Enrollment/Recruitment Challenges Faced During Year 4:

- **Enrollment Challenges**

Enrollment continued to improve in Y4. There were a high number of drop outs in Y4, Q1 (4 participants dropped out before completing the follow-up compared to only 2 participants in all previous quarters of the study combined), and so the informed consent document was modified to re-allocate compensation for study procedures and create a greater incentive for follow-up completion (participants now receive \$50 for the follow-up instead of the previous \$25). Due to the holiday season in Y4, Q2, many participants were expectedly rendered ineligible due to irregular sleep patterns and excessive alcohol use, however more than three times the number of participants signed consents during Y4, Q2 than during Y3, Q2. In addition, Y4, Q2 resulted in more than four times the amount of completers than in Y3, Q2 (13 completers vs. 3 completers). There were significant improvements in enrollment during Y4, Q3 due to the protocol modification allowing female participants to be dosed within either phase of the menstrual cycle (as long as they do not meet criteria for Premenstrual Dysphoric Disorder and/or moderate to severe Premenstrual Syndrome).

Consenting and screening procedures are ongoing. Enrollment has continued to increase and is nearing the quarterly goal. Including the study coordinator, five staff members are trained to give informed consent to date, increasing the study's weekly screening capacity.

- **Recruitment Challenges**

Recruitment metrics suggest that 36.6% of potential participants phone screened were deemed eligible to come in for an informed consent meeting (up from 18% in Y3). As discussed above, holiday alcohol use remained a barrier to recruitment during the winter months.

C.) Future Enrollment Strategies:

- **Recruitment and Outreach:**

Revised recruitment materials were recently submitted to the UCSF CHR and were approved on April 9, 2013. The revised recruitment materials focus on taglines and phrases that will attract participants most likely to meet our eligibility criteria during the holiday season due to the significant amount of rule-outs during this time due to sleep patterns and alcohol use. Outreach efforts planned for the immediate future include the continued distribution of posters, flyers, and postcards on the campuses of local universities as well as online advertisements.

- **Monthly Enrollment Projections:**

By the end of Year 4, a total of 118 participants completed study drug dosing procedures. In order to enroll 200 participants by the end of the study, we will need to enroll 7 participants per month until the end of August 2014. The study team is taking a variety of steps to reach this goal including increasing study staff (e.g. informed consenters, neuropsychological assessment administrators, and clinical interviewers) and improving recruitment materials to target common reasons for rule outs during the phone screening process.

**Subtask #6: Score and Analyze Data**

Study data has been scored and cleaned on an ongoing basis since the initiation of enrollment to shorten the cleaning and analysis timelines required during Y5. All data is QC'd and scored by trained and qualified study staff. Data Entry is ongoing and up to date.

**Other Accomplishments Completed During Year 4:**

- **Reporting:**

Ongoing reports have been submitted as follows:

- Safety listings are submitted to Actelion Pharmaceuticals on a monthly basis.
- Progress reports are submitted to the Department of Defense on a quarterly basis.
- Progress reports are submitted to the FDA on an annual basis.

- **Human and Animal Study Collaboration:**

The San Francisco (human study) and SRI International (animal study) teams met either monthly or biweekly via teleconference throughout Year 4 to share progress updates, scientific rationale, and future planning initiatives. An in-person collaborative meeting was hosted by SRI in August 2011 and the most recent meeting was hosted at the SFVAMC in September 2012, just after the conclusion of Year 3. An upcoming meeting is scheduled for October 2013. At each in-person meeting, members from each team gave presentations related to research rationale, progress, and future directions.

**Tasks 2 – 5:** Please refer to the attached report from Dr. Kilduff (Appendix 2) which details the progress made in reference to the animal studies.

**KEY RESEARCH ACCOMPLISHMENTS**

**Task 1 Accomplishments:**

- Revised informed consent documents and recruitment materials have been approved by UCSF CHR.
- All new study personnel (Study Coordinator, Recruiter, and Research Assistant) have been hired and trained on the study protocol and procedures.
- 118 eligible participants have been identified through recruitment and screening efforts and have undergone dosing procedures.
- Recruitment materials have been revised to increase phone screening success, expand inclusion criteria for women and boost enrollment.

#### Tasks 2 – 5 Accomplishments:

Please refer to the attached progress report from Dr. Kilduff (Appendix 2).

#### **REPORTABLE OUTCOMES**

Reportable outcomes related to Task 1 will not be available until Year 5. In keeping with our double-blind study design, we do not intend to open the blind on the human subjects study until we have reached our recruitment goal so that our study has enough power to detect statistically meaningful differences between groups. Because our study is enrolling healthy control subjects, at this time we feel there is little scientific value in analyzing sleep data on healthy controls, or other questions distal to our main research questions.

We do aim to report on our data as soon as possible once we've met our recruitment goal and are looking forward to presenting our findings in publications, research presentations and meeting presentations. As mentioned on page 5 of this report, our study data has been scored and cleaned on an ongoing basis since the initiation of enrollment to shorten the cleaning and analysis timelines required during Y5. All data is QC'd and scored by trained and qualified study staff. Data Entry is ongoing and up to date. Screening data (demographics information, height, weight, pre-dosing hematology, urine toxicology, pregnancy test results and blood chemistry), baseline data (sleep habits and caffeine use), inpatient eligibility data (urine toxicology, pregnancy test results), inpatient testing data (neuropsychological testing, vital signs and symptoms checklist), and follow up data (blood chemistry, adverse events reporting) are all up to date in our database and ready to be analyzed once we meet our recruitment goal.

Reportable outcomes related to Tasks 2 – 5 are noted in the attached progress report from Dr. Kilduff (Appendix 2). In addition, the following collaborative paper is under review:

Morairty SR, Wilk A, Lincoln W, Neylan TC, Kilduff TS. The Hypocretin/Orexin Antagonist Almorexant Promotes Sleep Without Impairment of Performance in Rats. In submission (Frontiers in Neuroscience).

#### **CONCLUSION**

Preclinical data indicate that animals treated with almorexant are easily aroused from sleep and are free of ataxia and other behavioral impairments. If this observation is confirmed in humans, it would have enormous implications for the management of disturbed sleep in both military and civilian populations. The purpose of this research is to test related hypotheses in both animals and humans. Enrollment of human subjects began during Year 2 and is expected to continue until August 2014. The findings from the animal component of the study were consistent with the hypothesis that disfacilitation of wake-promoting systems by almorexant results in less functional impairment than the general inhibition of neural activity produced by zolpidem (Appendix 2).

#### **APPENDICES**

Appendix 1: Human Study Protocol

Appendix 2: Animal Studies Progress Report

## Appendix 1: Human Study Protocol

## CLINICAL STUDY PROTOCOL

**Title:** Effect of a Hypocretin/Orexin Antagonist on Neurocognitive Performance

**Protocol number:** NEY-1413

**Protocol Version/Date:** Final Version 9.0 28 March 2013

**Phase:** Investigator-Initiated

**Investigational Drug:** Almorexant

**Investigator-Sponsor:** Thomas C. Neylan, M.D.  
Northern California Institute for Research and Education  
4150 Clement Street (116P)  
San Francisco, CA 94121

**Medical Monitor:** Frank Schoenfeld, MD  
Northern California Institute for Research and Education  
4150 Clement Street (116P)  
San Francisco, CA 94121




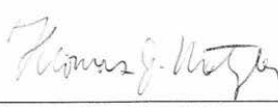

**Study Sites:** University of California, San Francisco  
Clinical and Translational Sciences Institute  
Clinical Research Center  
505 Parnassus Avenue  
San Francisco, CA 94143

San Francisco Department of Veterans Affairs Medical  
Center  
4150 Clement Street  
San Francisco, CA 94121

This clinical study will be conducted in accordance with Standard Operating Procedures (SOPs), current Good Clinical Practice (GCP) and the provisions of International Conference on Harmonization (ICH) Guidelines

---

**Protocol Approval**  
**NEY-1413**  
**Final Version 9.0 28 March 2013**

Investigator-Sponsor		4-18-2013
	Thomas Neylan, MD	Date
Co-Investigator		4/22/13
	Steven Batki, MD	Date
Co-Investigator		4-18-2013
	Kristin Samuelson, Ph.D.	Date
Biostatistician		4-18-2013
	Thomas Metzler, M.S.	Date
Study Coordinator		4/22/13
	Sarah Roth, B.A.	Date

**TABLE OF CONTENTS**

<b>ABBREVIATIONS .....</b>	<b>5</b>
<b>SYNOPSIS .....</b>	<b>7</b>
<b>1. INTRODUCTION .....</b>	<b>12</b>
1.1 Background .....	12
1.2 Rationale .....	13
<b>2. CLINICAL STUDY OBJECTIVES.....</b>	<b>14</b>
2.1 Primary Objectives.....	14
2.2 Secondary Objectives.....	14
<b>3. STUDY DESIGN .....</b>	<b>15</b>
3.1 Study Design Schematic .....	16
<b>4. SUBJECT SELECTION.....</b>	<b>17</b>
4.1 Subject Inclusion Criteria.....	17
4.2 Subject Exclusion Criteria .....	17
<b>5. STUDY DRUG HANDLING .....</b>	<b>19</b>
5.1 Allocation to Dosing Groups .....	19
5.2 Breaking the Blind .....	19
5.3 Dosing Adherence/Study Compliance.....	19
5.4 Drug Supplies.....	20
5.5 Drug Storage and Accountability.....	20
5.6 Concomitant Medications .....	20
<b>6. STUDY PROCEDURES .....</b>	<b>21</b>
6.1 Pre-Dosing Procedures.....	21
6.2 Study Dosing.....	24
<b>7. STUDY OUTCOMES AND SAFETY ASSESSMENTS .....</b>	<b>25</b>
7.1 Study Outcome Assessment Measures.....	26
7.2 Safety Assessment Measures .....	27
<b>8. ADVERSE EVENT REPORTING .....</b>	<b>28</b>
8.1 Adverse Event Definitions.....	28
8.2 Recording Requirements.....	29
8.3 Reporting of Adverse Events .....	29
<b>9. STATISTICAL METHODS/DATA ANALYSIS .....</b>	<b>31</b>
9.1 Study Endpoints .....	31
9.2 Sample Size Determination.....	32

9.3 Definition of Analysis Populations .....	33
9.4 Safety Analysis .....	33
<b>10. QUALITY CONTROL AND QUALITY ASSURANCE .....</b>	<b>33</b>
<b>11. DATA HANDLING, RECORD-KEEPING, AND CONFIDENTIALITY .....</b>	<b>33</b>
11.1 Data Recording/Case Report Forms.....	33
11.2 Record Maintenance and Retention .....	34
11.3 Confidentiality .....	35
<b>12. ETHICS .....</b>	<b>36</b>
12.1 Institutional Review Board (IRB) Approval .....	36
12.2 Ethical and Scientific Conduct of the Clinical Study.....	37
12.3 Subject Informed Consent.....	37
<b>13. EARLY DISCONTINUATION CRITERIA .....</b>	<b>38</b>
<b>14. RISKS AND BENEFITS .....</b>	<b>38</b>
<b>15. STUDY PERSONNEL .....</b>	<b>41</b>
<b>14. REFERENCES .....</b>	<b>43</b>

**ABBREVIATIONS**

AE	Adverse Event
AASM	American Academy of Sleep Medicine
BzRAs	Benzodiazepine Receptor Agonists
CRC	Clinical Research Center
CCRC	University of California, San Francisco Clinical Translational and Sciences Institute Inpatient Clinical Research Center
UCSF CHR	University of California, San Francisco Committee on Human Research
CNS	Central Nervous System
CPT	Conners' Continuous Performance Test II
CRF	Case Report Form
DMP	Data Management Plan
DS	Digit Span Subtest of the Wechsler Adult Intelligence Scale Fourth Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision
EEG	Electroencephalogram
FDA	Food and Drug Administration
GABA	Gamma-Aminobutyric Acid
GCP	Good Clinical Practice
GP	Grooved Pegboard Motor Test
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IQ	Intelligence Quotient
IRB	Institutional Review Board
MWT	Maintenance of Wakefulness Test
NREM	Non-Rapid Eye Movement
ORP HRPO	Federal Office of Research Protections Human Research Protection Office
P-A	Paired Associates Learning Task
PMDD	Premenstrual Dysphoric Disorder
PMS	Premenstrual Syndrome
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
PSST	Premenstrual Symptoms Screening Tool
PVT	Psychomotor Vigilance Test
QC	Quality Control

R&D Committee	Veterans Affairs Research and Development Committee
REM	Rapid Eye Movement
RAVLT	Rey Auditory Verbal Learning Test
SAE	Serious Adverse Event
SC	Symptom Checklist
SCID	Structured Clinical Interview for DSM-IV TR Axis I Disorders
SFDVAMC	San Francisco Department of Veterans Affairs Medical Center
SSS	Stanford Sleepiness Scale
Stroop	Stroop Color-Word Test
Towers	Tower Test from Delis-Kaplan Executive Function System
USAMRMC	U.S. Army Medical Research Materiel Command
WAIS-IV	Wechsler Adult Intelligence Scale Fourth Edition
WASO	Wake after Sleep Onset
WMS	Wechsler Memory Scale

**SYNOPSIS**

<b>Protocol Number:</b>	NEY-1413
<b>Study Title:</b>	A Double-Blind, Placebo-Controlled, Randomized, Parallel-Group Study Comparing the Effect of a Novel Hypocretin/Orexin Antagonist (Almorexant) Versus a Standard Hypnotic (Zolpidem) and Placebo on Neurocognitive Performance
<b>Number of Sites:</b>	1
<b>Treatment Duration:</b>	One-time Dose
<b>Study Duration:</b>	10 days, with a follow-up visit within 5 – 12 days of dosing
<b>Study Population:</b>	216 healthy male and female volunteers
<b>Rationale:</b>	In recent years, there has been increased focus on neurocognitive effects of hypnotic medications that adversely affect behavior during unanticipated awakenings during the night. Concerns regarding untoward effects of hypnotics during the sleep period have led to a Food and Drug Administration (FDA) class warning for all hypnotic drugs. These concerns are particularly relevant to the personnel of the military and those in other professions who have an occupational risk of poor sleep and who are expected to perform without impairment upon awakening. Almorexant is a hypocretin/orexin antagonist with a novel mechanism of action that has shown promise as an effective hypnotic. Preclinical data demonstrate that animals treated with almorexant are easily aroused from sleep and behave free of ataxia and other impairment. If this observation is confirmed in humans, it will have substantial implications for the management of disturbed sleep in both military and civilian populations.
<b>Study Objectives:</b>	To compare neurocognitive performance at peak concentration at midpoint during the habitual wake period in subjects randomized to almorexant 100mg, almorexant 200mg, zolpidem 10mg, or placebo.
<b>Study Design:</b>	The study will take place at the San Francisco Department of Veterans Affairs Medical Center (SFDVAMC) and the University of California, San Francisco Clinical Translational and Sciences Institute inpatient Clinical Research Center (CCRC). The study will involve healthy volunteers who are considered normal sleepers per the Research Diagnostic Criteria for Normal Sleepers and who are free of medical disorders and specified psychiatric disorders. After informed consent has been obtained and eligibility has been confirmed, subjects will be scheduled for the 10-day study period. During the first seven days of the study period (the sleep/wake

	<p>monitoring period), subjects will be asked to maintain a sleep diary and wear a wrist activity monitor (actigraph) 24 hours per day. Subjects will be admitted to the CCRC on the eighth day of the study period, two days prior to study drug administration. Subjects' sleep will be monitored with polysomnography (PSG) during each night on the CCRC, and subjects will continue to maintain a sleep diary and wear an actigraph during the three-day hospital stay. Subjects will be randomized in a double-blind fashion to one of four groups (almorexant 100mg, almorexant 200mg, zolpidem 10mg, or placebo). Study drug will be provided to a nurse on the CCRC by an unblinded research pharmacist. The nurse and all other study personnel will remain blinded when study drug is dispensed to subjects. Following dosing, subjects will be accompanied by study personnel and instructed to remain awake. Neurocognitive, objective alertness, and subjective symptom assessments will be administered for several hours following dosing. Adverse events (AEs) will be assessed at the time of admission to the CCRC and on each day of the subject's stay in the CCRC. Subjects will be debriefed and discharged from CCRC on the morning of the fourth day on the unit. They will be required to return to the CRC at the SFDVAMC within 5 – 12 days of dosing for a safety lab test (liver function).</p>
<b>Inclusion Criteria:</b>	<ol style="list-style-type: none"> <li>1.) Male and female subjects between the ages of 19 and 39 determined to be physically healthy by physical exam and laboratory assessments;</li> <li>2.) Habitual wake time between 0600 hr and 0900 hr maintained within the past month;</li> <li>3.) Habitual bedtime between 2200 hr and 0100 hr maintained within the past month;</li> <li>4.) Body Mass Index (BMI) &gt;18 and &lt; 28 kg/m<sup>2</sup>;</li> <li>5.) Ability to communicate well with the Investigator and to understand the study requirements.</li> </ol>
<b>Exclusion Criteria:</b>	<ol style="list-style-type: none"> <li>1.) Diagnosis of a sleep disorder within two years of screening or current sleep disturbance as suggested by a global score of &gt; 5 on the Pittsburgh Sleep Quality Index (PSQI);</li> <li>2.) Current presence of two or more risk categories on the Berlin Questionnaire for sleep apnea and overnight oximetry showing 10 desaturation events per hour or other results which are, in the judgment of the Investigator-Sponsor, suggestive of sleep apnea.</li> <li>3.) A current or lifetime diagnosis of any psychiatric disorder with psychotic features, major depression, bipolar disorder, panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, generalized anxiety disorder, dysthymia, or agoraphobia without panic disorder, or current diagnosis of</li> </ol>

	<p>depressive disorder not otherwise specified, assessed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) Axis I Disorders (SCID);</p> <ol style="list-style-type: none"> <li>4.) A current diagnosis of alcohol or substance abuse or dependence or a history of alcohol or substance abuse or dependence within the past year, assessed using the SCID;</li> <li>5.) Subjects who are pregnant, lactating, or planning to become pregnant or subjects who are not willing to use an acceptable form of birth control during the study;</li> <li>6.) Lifetime history of brain injury (including concussions, mild traumatic brain injuries, or loss of consciousness for <math>\geq 10</math> minutes which resulted in the development of persistent symptoms lasting <math>\geq 1</math> month), stroke, brain hemorrhage, seizures (not including infantile febrile seizures), epilepsy, or brain infection caused by meningitis, encephalitis, or any other infectious agent.</li> <li>7.) Systemic illness affecting central nervous system (CNS) function;</li> <li>8.) Cardiovascular disease (to include but not limited to arrhythmias, valvular heart disease, congestive heart failure, history of myocardial infarction or family history of sudden cardiac death), hypertension, or hypercholesterolemia;</li> <li>9.) Asthma or other reactive airway diseases;</li> <li>10.) Hepatic impairment (Child-Pugh A, B, C);</li> <li>11.) Any other chronic or unstable medical conditions;</li> <li>12.) Current use of statins, ketoconazole, prescription or over-the-counter medications or herbal supplements containing psychoactive properties or stimulants in the judgment of the Investigator-Sponsor or Medical Monitor;</li> <li>13.) Treatment with another investigational drug;</li> <li>14.) Current daily use of any other medication unless specifically approved by the Investigator-Sponsor;</li> <li>15.) Consumption of grapefruit (including grapefruit juice) or treatment with moderate or strong inhibitors of cytochrome P450 3A4 (CYP3A4) within one week prior to randomization;</li> <li>16.) Treatment with drugs metabolized by CYP2D6 isoenzyme with a narrow therapeutic index within one week prior to randomization;</li> <li>17.) Self-reported regular nicotine use within the past 30 days involving <math>&gt; 4</math> cigarettes per week or <math>&gt; 2</math> cigarettes per day;</li> <li>18.) Self-reported consumption of alcohol within the past 30 days of <math>&gt; 14</math> standard drinks per week or <math>\geq 5</math> standard drinks on any day (men), or <math>&gt; 7</math> standard drinks per week or <math>\geq 4</math> standard drinks on any day (women).</li> </ol>
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	<p>19.) Use of opioids, benzodiazepines, amphetamines, cocaine, cannabis, or any other illicit drugs within 30 days of screening by self report or a urine toxicology screen;</p> <p>20.) Known liver disease or abnormal liver function tests assessed at the time of screening;</p> <p>21.) Self-reported regular caffeine use in excess of 400 mg per day on average within six months of screening;</p> <p>22.) Habitual long sleepers (&gt; 9 hours) or short sleepers (&lt; 5 hours);</p> <p>23.) Shift work within one month prior to the screening visit or planned shift work during the study;</p> <p>24.) Subjects who have traveled &gt; 3 time zones within one week prior to the screening visit or any other visit;</p> <p>25.) Known hypersensitivity or contraindication to any excipients of the drug formulation.</p>
<b>Outcome Measures:</b>	<p><u>Primary Endpoints:</u></p> <ol style="list-style-type: none"> <li>1.) A comparison between groups on performance on the following neurocognitive measures: Rey Auditory Verbal Learning Test (RAVLT), Digit Span subtest of the Wechsler Adult Intelligence Scale IV (DS), Grooved Pegboard motor test, Paired-Associates subtest of the Wechsler Memory Scale (P-A), Stroop Color-Word Test (Stroop), Tower Test from Delis-Kaplan Executive Function System (D-KEFS Tower), Psychomotor Vigilance Test (PVT), and Conners' Continuous Performance Test II (CPT).</li> <li>2.) A comparison between groups on latency to sleep onset measured by Maintenance of Wakefulness Tests (MWT) at 30 minutes and 150 minutes post-dose.</li> <li>3.) A comparison between groups on low frequency EEG power during artifact free wake time as measured during MWTs.</li> </ol> <p><u>Secondary Endpoints:</u></p> <ol style="list-style-type: none"> <li>1.) A comparison between groups on latency to sleep onset measured by MWTs at 270 and 390 minutes post-dose.</li> <li>2.) A comparison between groups on Stanford Sleepiness Scale (SSS) scores.</li> </ol> <p><u>Covariates:</u></p> <ol style="list-style-type: none"> <li>1.) Polysomnography (PSG) – Total Sleep Time on the night prior to the day of dosing.</li> <li>2.) Actigraphy – Average sleep duration.</li> </ol>
<b>Statistical Considerations:</b>	<p>It is hypothesized that subjects receiving zolpidem 10mg will show greater impairment in neurocognitive performance compared to subjects receiving placebo, almorexant 100mg, or almorexant</p>

	<p>200mg. This hypothesis will be tested by comparing groups on post-medication performance tests using pre-medication test scores as covariates. Where multiple administrations of a performance test are given either pre-or post-medication, mixed effects models will be used, with the group by time (i.e., pre- vs. post-medication) interaction effect serving as the test of the hypothesis. Where a test is administered only once pre- and post-medication, the statistical test will be a one-way ANCOVA comparing mean scores on the four groups, with the pre-medication test score serving as the covariate. Planned comparisons will be conducted to compare the zolpidem 10mg group with placebo, almorexant 100mg, and almorexant 200mg separately. P-value adjustments will be made for multiple endpoint variables within any given neurocognitive domain using a step-down non-parametric re-sampling-based procedure. Primary analyses will be intent-to-treat, including all subjects randomized regardless of dropout or missing data status. Missing data will be carefully characterized and multiply imputed if necessary.</p>
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## 1. INTRODUCTION

### 1.1 Background

In recent years, there has been increased focus on cognitive side effects associated with sleep-inducing medications that may contribute to unusual behavior during unexpected awakenings during the night. Concerns regarding these side effects have led to a Food and Drug Administration (FDA) class warning for all sleep-inducing medication. These concerns are particularly important to the military and other professions that have an occupational risk of poor sleep and being unexpectedly awakened with an expectation to perform without impairment.

Almorexant is a hypocretin/orexin antagonist with a novel mechanism of action that has shown promise as an effective hypnotic. Hypocretin/orexin is a neuropeptide system that stimulates arousal and is involved in sleep regulation. Disruption of the hypocretin/orexin system has been shown to result in the sleep disorder narcolepsy in both animals and humans, indicating that this system is part of the intricate sleep/wakefulness regulatory network. Hypocretin receptors are found in many brain regions, although receptor expression is weak in the cortex and high in brain regions associated with arousal state regulation, particularly the histaminergic, serotonergic, noradrenergic and cholinergic wake-promoting systems. Since the hypocretin peptides are excitatory throughout the brain, hypocretin antagonists work by blocking this excitation rather than producing a generalized inhibition. To the contrary, benzodiazepine receptor agonists (BzRAs) such as zolpidem affect gamma-aminobutyric acid (GABA<sub>A</sub>) receptors which have widespread distribution in the central nervous system (CNS), particularly in the cerebral cortex. BzRAs therefore cause a general inhibition of neural activity (2).

#### 1.1.1 Preclinical Background

Preclinical data demonstrate that almorexant produces a profile that is unique among currently marketed hypnotic medications. For example, preliminary study results in rats treated with one of three doses (10mg/kg, 30mg/kg, and 100mg/kg) of almorexant, zolpidem or placebo in the middle of the dark active period (six hours after lights offset) demonstrated that the 30mg/kg and 100mg/kg doses of almorexant and zolpidem increased non-rapid eye movement (NREM) sleep for several hours after dosing, whereas 10mg/kg of almorexant had a more transient effect. All three doses of almorexant increased rapid eye movement (REM) sleep while REM was suppressed by zolpidem. Consequently, the REM-NREM ratio was unchanged relative to vehicle in animals treated with almorexant, but zolpidem produced a decreased REM-NREM ratio which is characteristic of BzRAs. When cumulative effects were assessed over the entire six-hour post-treatment period, it was evident that almorexant produced a dose-dependent decrease of wake and a dose-dependent increase in both NREM and REM sleep. This profile of a proportional increase of REM and NREM sleep appears to be unique among currently marketed hypnotic medications (3).

Additionally, almorexant appears to have few side-effects on regulated physiological systems. Preliminary studies comparing the effects of varying doses of almorexant, zolpidem, and placebo on core body temperature in rats revealed that zolpidem-treated animals experienced a significant and prolonged change in core body temperature post-

treatment, but there was relatively little change in core body temperature associated with any dose of almorexant (3).

In studies involving somnolent rats treated with almorexant, the rats showed an immediate reversibility of the hypnotic effect with no impairment on motor performance tasks (3). If similar observations are confirmed in humans, there will be enormous implications for the management of disturbed sleep in both military and civilian populations.

### *1.1.2 Clinical Background*

Because hypocretins are implicated in coordinating states of wakeful vigilance, there has been a rapid development of small molecule hypocretin 1 and hypocretin 2 antagonists for possible use in insomnia. At present, there are robust drug discovery programs for hypocretin1/hypocretin 2 antagonists sponsored by Actelion, Glaxo-Smith Kline, Merck, Banyu, Sanofi-Aventis, and Janssen. In 2007, Actelion presented results of a multi-site, double-blind placebo controlled trial in insomnia patients examining the effects of 50mg, 100mg, 200mg, and 400mg doses of almorexant at bedtime. The results showed significant improvement in sleep efficiency and reduced wake after sleep onset (WASO) at doses of 100mg and higher (4). There was no occurrence of cataplexy at any of the dosages used. Almorexant has an elimination half-life of 1.4 hours and effects on sleep electroencephalography (EEG) were absent after 6.5 hours (3).

Almorexant was well-tolerated in studies completed to date, including nineteen Phase I studies in healthy and hepatically impaired subjects, two dose-finding studies in adult and elderly patients with primary insomnia, and one Phase III study in primary insomnia. 519 healthy and hepatically impaired subjects were exposed to at least one dose of almorexant in Phase I studies. 633 subjects with primary insomnia have been exposed to at least one dose of almorexant in completed studies. Maximum exposure was up to 400mg daily for 1 day or up to 200mg for 16 days. 166 patients with primary insomnia received 200mg for at least 14 days, and 176 received 100mg for at least 14 days. The most frequently reported adverse events with almorexant were headache, fatigue, dizziness, and somnolence (40).

## **1.2 Rationale**

At appropriate doses, all currently available FDA-approved prescription sleep-inducing agents induce restorative sleep. However, they also exert substantial performance-impairing effects at peak concentration in multiple domains of neurocognitive function. For example, multiple studies have shown impairment in driving within the six-hour window after ingesting zolpidem (6, 7). Other studies have documented impairment in balance and postural tone within two hours of taking zolpidem (8). Furthermore, there is solid evidence that at peak concentration, currently available sleep-inducing agents significantly impair the ability to consolidate new memories (9-12). This evidence therefore precludes the use of sleep-inducing agents under operational conditions in which individuals might be called upon to perform without impairment after taking the agent, which is particularly relevant to populations involved in military combat. Further,

there is an enormous accumulation of data linking disturbed sleep to a wide range of outcomes including daytime fatigue (13-15), impaired concentration and attention (16-19), increased risk for accidents and injuries (20, 21), worsened quality of life (22), increased aggression (23-26), and increased use of alcohol (27, 28). Several studies have also demonstrated that disturbed sleep is a potent risk factor for later onset development of major depression, panic disorder, alcohol, and substance abuse (27-30). Therefore, an effective treatment for sleep disturbances that can be safely utilized in deployed military personnel in combat operations without performance-impairing effects has the potential for improving the success of combat operations, inoculating soldiers against battlefield stress-related psychiatric illnesses, and preserving the psychological health of the soldiers throughout the full deployment lifecycle. The availability of such a treatment would also have a positive impact on the overall quality of life, physical, and psychological well being of the civilian population.

The study discussed in this protocol will involve a double-blind, placebo-controlled, randomized, parallel-groups study design and will involve a one-time oral administration of one of four dosing options to healthy volunteers: almorexant 100mg, almorexant 200mg, zolpidem 10mg, and placebo. These dosages have demonstrated favorable safety profiles in clinical trials (5). Subjects will be dosed at the average midpoint of the habitual wake period. Neurocognitive performance assessments will be administered at the time of peak plasma concentration. The study will establish whether almorexant is superior to zolpidem and placebo regarding neurocognitive performance at the estimated peak plasma concentration.

## **2. CLINICAL STUDY OBJECTIVES**

### **2.1 Primary Objectives**

Primary endpoints are listed below:

- 1.) A comparison between groups on performance on the following neurocognitive measures: Rey Auditory Verbal Learning Test (RAVLT), Digit Span subtest of the Wechsler Adult Intelligence Scale IV (DS), Grooved Pegboard motor test (GP), Paired-Associates subtest of the Wechsler Memory Scale (P-A), Stroop Color-Word Test (Stroop), Tower Test from Delis-Kaplan Executive Function System (D-KEFS Tower), Psychomotor Vigilance Test (PVT), and Conners' Continuous Performance Test II (CPT).
- 2.) A comparison between groups on latency to sleep onset measured by Maintenance of Wakefulness Tests (MWT) at 30 minutes and 150 minutes post-dose.
- 3.) A comparison between groups on low frequency EEG power during artifact free wake time as measured during MWTs.

### **2.2 Secondary Objectives**

Secondary endpoints are listed below:

- 1.) A comparison between dosing groups on latency to sleep onset measured by MWTs at 270 and 390 minutes post-dose.
- 2.) A comparison between dosing groups on Stanford Sleepiness Scale (SSS) scores.

The following outcomes will be analyzed as covariates:

- 1.) Polysomnography (PSG) - Total Sleep Time on the night prior to the day of dosing.
- 2.) Actigraphy – Average sleep duration.

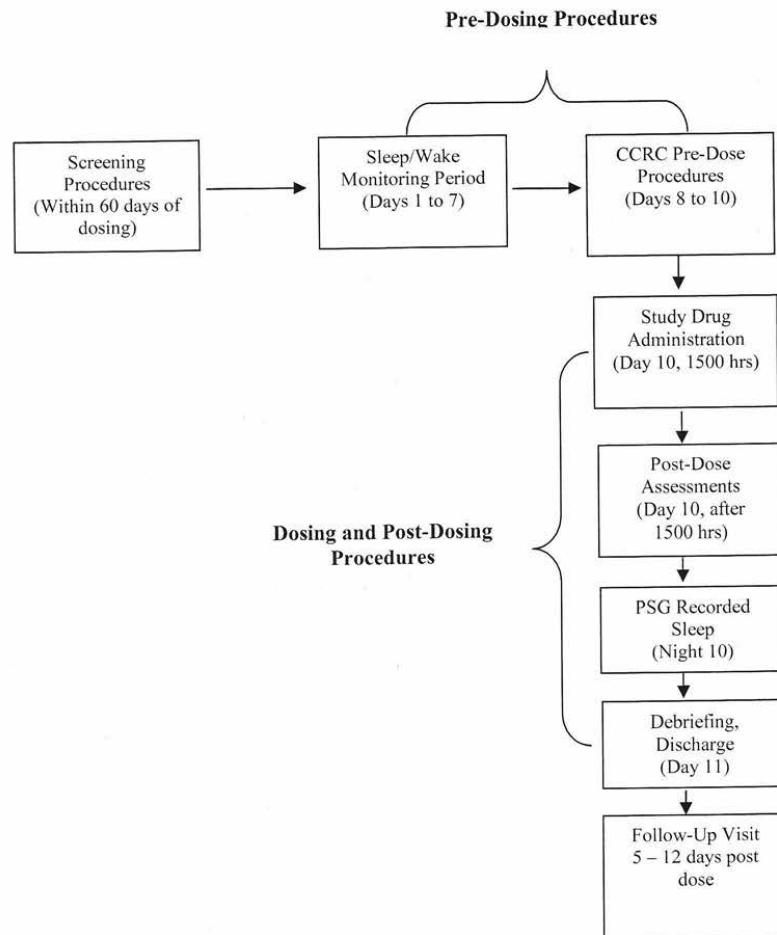
### 3. STUDY DESIGN

The study will take place at the San Francisco Department of Veterans Affairs Medical Center (SFDVAMC) and the University of California, San Francisco Clinical Translational and Sciences Institute inpatient Clinical Research Center (CCRC). The study will involve healthy volunteers who are considered normal sleepers per the Research Diagnostic Criteria for Normal Sleepers (1) as listed below:

- 1.) Subject has no complaints of sleep disturbance or daytime symptoms attributable to unsatisfactory sleep.
- 2.) Subject has a routine sleep/wake schedule characterized by regular bedtimes and rising times.
- 3.) There is no evidence of a sleep-disruptive medical or mental disorder.
- 4.) There is no evidence of sleep disruption due to a substance exposure, use, abuse, or withdrawal.
- 5.) There is no evidence of a primary sleep disorder.

Subjects will also be free of medical disorders and specified psychiatric disorders. After informed consent has been obtained and eligibility has been confirmed, subjects will be instrumented with wrist actigraphs to record their sleep/wake patterns for seven days; subjects will also be asked to complete a sleep diary during this one-week time period. Subjects will be admitted to the CCRC on the day after completion of the one-week sleep/wake monitoring period and two days prior to drug administration. Subjects' sleep will be monitored with PSG during each night at the CCRC, and sleep apnea will be screened for during the first night of PSG. Subjects will continue to maintain a sleep diary and wear an actigraph while at the CCRC. Subjects will be randomized in a double-blind fashion to one of four groups (almorexant 100mg, almorexant 200mg, zolpidem 10mg, or placebo). An unblinded research pharmacist will provide study drug to a nurse at the CCRC for dispensing. The nurse and all other study personnel will remain blinded when study drug is dispensed to subjects. Following dosing, subjects will be accompanied by study personnel and instructed to remain awake. Neurocognitive, objective alertness, and subjective symptom assessments will be administered at regular intervals for several hours following dosing. Adverse events (AEs) will be assessed at the time of admission to the CCRC and on each day of the subject's stay in the CCRC. Subjects will be debriefed and discharged from the CCRC during the morning of the fourth day on the unit. They will be required to return to the SFDVAMC within 5 – 12 days of dosing for a safety lab test (liver function).

### 3.1 Study Design Schematic



#### **4. SUBJECT SELECTION**

Medically healthy men and women ages 19-39 (N = 216) will be recruited from newspaper advertisements, web based postings, websites, and flyers posted in various university and community sites. The age range is restricted to an upper limit of 39 years as a result of research showing a change in middle-aged individuals (defined as 40+ years of age) in terms of total sleep time and other sleep parameters that can affect performance outcomes independent of sleep deprivation and/or drug administration, which could therefore introduce a substantial source of error variance into the study (31). Interested potential subjects will be contacted by the study recruiter. If potential subjects agree, a 15 – 30 minute phone discussion will take place to determine whether they might be a match for the study. If the phone conversation indicates that the potential subjects may be a match for the study and they are still interested, they will be scheduled to meet with the study coordinator or another qualified study team member in person at the SFDVAMC for informed consent and further eligibility procedures.

##### **4.1 Subject Inclusion Criteria**

Subjects must meet all inclusion criteria in order to be eligible for the study:

- 1.) Male and female subjects between the ages of 19 and 39 determined to be physically healthy by physical exam and laboratory assessments;
- 2.) Habitual wake time between 0600 hr and 0900 hr maintained within the past month;
- 3.) Habitual bedtime between 2200 hr and 0100 hr maintained within the past month;
- 4.) Body Mass Index (BMI)  $>18$  and  $<28 \text{ kg/m}^2$ ;
- 5.) Ability to communicate well with the Investigator and to understand the study requirements.

##### **4.2 Subject Exclusion Criteria**

Any of the following criteria will exclude the subject from entering the study:

- 1.) Diagnosis of a sleep disorder within two years of screening or current sleep disturbance as suggested by a global score of  $>5$  on the Pittsburgh Sleep Quality Index (PSQI) (43);
- 2.) Current presence of two or more risk categories on the Berlin Questionnaire (42) for sleep apnea and overnight oximetry showing 10 desaturation events per hour or other results which are, in the judgment of the Investigator-Sponsor, suggestive of sleep apnea.
- 3.) A current or lifetime diagnosis of any psychiatric disorder with psychotic features, major depression, bipolar disorder, panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, generalized anxiety disorder, dysthymia, or agoraphobia without panic disorder, or current diagnosis of depressive disorder not otherwise specified, assessed using the Structured Clinical Interview for DSM-IV TR Axis I Disorders (SCID) (41);

- 4.) A current diagnosis of alcohol or substance abuse or dependence or a history of alcohol or substance abuse or dependence within the past year, assessed using the SCID (41);
- 5.) Subjects who are pregnant, lactating, or planning to become pregnant or subjects who are not willing to use an acceptable form of birth control during the study;
- 6.) Lifetime history of brain injury (including concussions, mild traumatic brain injuries, or loss of consciousness for  $\geq 10$  minutes which resulted in the development of persistent symptoms lasting  $\geq 1$  month), stroke, brain hemorrhage, seizures (not including infantile febrile seizures), epilepsy, or brain infection caused by meningitis, encephalitis, or any other infectious agent.
- 7.) Systemic illness affecting central nervous system (CNS) function;
- 8.) Cardiovascular disease (to include but not limited to arrhythmias, valvular heart disease, congestive heart failure, myocardial infarction or family history of sudden cardiac death), hypertension, or hypercholesterolemia;
- 9.) Asthma or other reactive airway diseases;
- 10.) Hepatic impairment (Child-Pugh A, B, C);
- 11.) Any other chronic or unstable medical conditions;
- 12.) Current use of statins, ketoconazole, prescription or over-the-counter medications or herbal supplements containing psychoactive properties or stimulants in the judgment of the Investigator-Sponsor or Medical Monitor;
- 13.) Treatment with another investigational drug;
- 14.) Current daily use of any other medication unless specifically approved by the Investigator-Sponsor;
- 15.) Consumption of grapefruit (including grapefruit juice) or treatment with moderate or strong inhibitors of cytochrome P450 3A4 (CYP3A4) within one week prior to randomization;
- 16.) Treatment with drugs metabolized by CYP2D6 isoenzyme with a narrow therapeutic index within one week prior to randomization;
- 17.) Self-reported regular nicotine use within the past 30 days involving  $> 4$  cigarettes per week or  $> 2$  cigarettes per day;
- 18.) Self-reported consumption of alcohol within the past 30 days of  $> 14$  standard drinks per week or  $\geq 5$  standard drinks on any day (men), or  $> 7$  standard drinks per week or  $\geq 4$  standard drinks on any day (women).
- 19.) Use of opioids, benzodiazepines, amphetamines, cocaine, cannabis, or any other illicit drugs within 30 days of screening by self report or a urine toxicology screen;
- 20.) Known liver disease or abnormal liver function tests assessed at the time of screening;
- 21.) Self-reported regular caffeine use in excess of 400 mg per day on average within six months of screening;
- 22.) Habitual long sleepers ( $> 9$  hours) or short sleepers ( $< 5$  hours);
- 23.) Shift work within one month prior to the screening visit or planned shift work during the study;
- 24.) Travel of  $> 3$  time zones within one week prior to the screening visit or any other visit;

- 25.) Known hypersensitivity or contraindication to any excipients of the drug formulation.

## **5. STUDY DRUG HANDLING**

### **5.1 Allocation to Dosing Groups**

Subjects will be randomly assigned to one of four dosing groups in a 1:1:1:1 ratio: almorexant 100mg, almorexant 200mg, zolpidem 10mg, or placebo. Randomization will be stratified based on gender and caffeine use. Subjects will dose one time on Study Day 10 at 1500 hrs according to their assigned dosing group.

Almorexant (100mg and 200mg) is currently being investigated in a comprehensive Phase III program. Results indicate that almorexant was well-tolerated in the initial Phase III study. Further Phase III studies to evaluate long-term efficacy and safety are in preparation (4).

Zolpidem 10mg is an imidazopyridine class sedative hypnotic which received original United States market approval under the brand name Ambien® in 1992.

### **5.2 Breaking the Blind**

The blind will be maintained through study completion except for cases of breaking the blind due to emergency medical necessity. In situations in which the CCRC nursing staff or other study personnel determines that it might be necessary to break the blind, he/she will be instructed to contact the Investigator-Sponsor or Medical Monitor. If approval is granted by the Investigator-Sponsor or Medical Monitor, the CCRC nurse will be authorized to contact the research pharmacist at the CCRC. The research pharmacist will maintain a master randomization list and he/she or an authorized designee will be available to break the blind if necessary.

### **5.3 Dosing Adherence/Study Compliance**

Since only one dose will be administered to subjects by a nurse at the CCRC, deviations from the scheduled dosing regimen are not anticipated.

During the sleep-wake monitoring period which will take place throughout the week prior to admission to the CCRC, subjects will be required to maintain regular wake times between 0600 hr and 0900 hr and bedtimes between 2200 hr and 0100 hr. Additionally, subjects will be asked to avoid recreational drug use, naps, the consumption of grapefruit or grapefruit juice, alcohol, and/or nicotine. Subjects will also be asked to maintain stable caffeine use and to avoid crossing more than three time zones. Actigraphs will be utilized to monitor the subjects' sleep-wake patterns and will therefore serve as a check for compliance with the prescribed sleep regimen. Subjects will maintain daily sleep diaries during the 10-day study period which will capture the following items: lights out and wake clock times, estimated sleep latency, wake time in minutes after sleep onset, rating

of sleep quality on a scale of 1-100, caffeine use, and atypical events. Actigraphy and sleep diary data will be reviewed upon admission to the CCRC to determine compliance with the required sleep/wake schedule. An additional urine toxicology screening will be administered at the time of admission to the CCRC to rule out recent recreational drug use, and females will receive a urine pregnancy test at this time.

## **5.4 Drug Supplies**

### *5.4.1 Formulation and Packaging*

Actelion Pharmaceuticals Ltd. will provide almorexant 100 mg tablets, zolpidem 10 mg capsules, and matching placebo tablets and capsules. A double dummy design will be employed which will result in each subject receiving two tablets and one capsule. Study drug will be provided in bulk and will be shipped directly to the research pharmacy at the CCRC.

### *5.4.2 Preparing and Dispensing*

The research pharmacist in the CCRC will maintain a copy of the randomization schedule and will receive the subject's randomization assignment at the time of hospital admission. The research pharmacist will dispense the assigned study drug to the nurse who will be administering the drug to the randomized subject.

### *5.4.3 Drug Administration*

After obtaining the appropriate study drug from the research pharmacy, a CCRC nurse will administer the drug to the subject.

## **5.5 Drug Storage and Accountability**

All drug products will be stored at the recommended temperature (room temperature at a maximum of 25°C). Site personnel and study monitors will perform regular checks to document that the study drug is stored appropriately and is within the defined expiration period at all times. A drug accountability log will be completed by the research pharmacist when study drug is received and dispensed to subjects. Any unused drug will be destroyed at the conclusion of the study.

## **5.6 Concomitant Medications**

Medication use will be assessed at screening. Concomitant medications will also be assessed when the subject arrives at the CCRC on Day 8, on each subsequent day in the CCRC (Days 9, 10, and 11), and at follow-up. All concomitant medications will be recorded in the source documents and transcribed onto the Case Report Forms (CRFs).

### *5.6.1 Disallowed Concomitant Medications and Dietary Restrictions*

Use of statins, prescription or over-the-counter medications containing psychoactive properties or stimulants is exclusionary and is also prohibited during the study period. Subjects will be required to maintain stable caffeine consumption of 200 mg per day or less during the study. Alcohol, recreational drug, and nicotine use is prohibited during the 10 day study period. Consumption of grapefruit (including grapefruit juice) or treatment with moderate or strong inhibitors of cytochrome P450 3A4 (CYP3A4) within one week prior to randomization is prohibited.

## **6. STUDY PROCEDURES**

### **6.1 Pre-Dosing Procedures**

#### **Screening**

The study coordinator or another qualified, trained study team member will obtain informed consent from each potential subject prior to the initiation of eligibility procedures. During the informed consent meeting, the study will be explained and the subject's questions will be answered. Subjects will be allowed to take as much time as they need to make a decision and will be given the option of discussing their decision with their family, friends, or other healthcare providers.

- Physical Exam, Medical History, and Prior/Concomitant Medications Assessment (performed by a nurse practitioner at the SFVAMC CRC).
- Laboratory Analysis of Blood and Urine Samples: A urine sample and approximately 20ccs of blood will be collected for laboratory tests which will include a serum chemistry panel, liver function tests (including albumin), thyroid function tests, prothrombin time, complete blood count and differential, urine toxicology screen, and a urine pregnancy test (in women of childbearing potential). If lab values are out of range, subjects may be asked to repeat the blood draw for a retest to confirm their medical health.
- Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID [41]), performed by a trained mental health clinician
- Self-report Berlin Questionnaire (42) to determine likelihood of sleep disordered breathing. If subjects have two or more positive scoring categories, they will also be monitored with pulse oximetry.
- Self-report Pittsburgh Sleep Quality Index (PSQI [43])
- The Premenstrual Symptoms Screening Tool (PSST) to determine if female participants meet criteria for Premenstrual Dysphoric Disorder (PMDD) and/or moderate to severe PMS. For all females who meet criteria for PMDD and/or moderate to severe PMS, Days 8-10 will be scheduled to coincide with the follicular phase of the menstrual cycle (PSST [54]).
- Review of Inclusion/Exclusion Criteria

All screening assessments will be performed at the SFDVAMC, including the collection of blood and urine samples and laboratory analysis. Dosing with study drug must take

place within 60 days of when the screening assessments were administered. Screening assessments which were administered > 60 days prior to scheduled dosing will have to be repeated before subjects will be allowed to dose with study drug.

During the screening period the Vocabulary Subtest of the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV [48]) will be administered for the purpose of obtaining an IQ measure to ensure that all dosing groups are matched on intelligence. Vocabulary Subtest results will not be used to determine eligibility.

#### **Sleep/Wake Monitoring (Days 1 to 7)**

A seven-day sleep/wake baseline monitoring period will be scheduled for subjects who meet all inclusion and exclusion criteria. For female subjects, the baseline monitoring period will be scheduled such that Days 8 - 10 correspond to either the follicular or luteal phase of the menstrual cycle. For all females who meet criteria for PMDD and/or moderate to severe PMS, Days 8-10 will be scheduled to coincide with the follicular phase of the menstrual cycle. Prior to the start of the baseline week, a practice version of the PVT will be administered. Subjects will be asked to wear wrist actigraphs 24 hours per day on each day of the seven day monitoring period, and they will also be asked to abide by the following instructions:

- Adhere to a consistent wake schedule of 0600 hrs – 0900 hrs and a lights out schedule of 2200 hrs – 0100 hrs.
- Avoid nicotine and recreational drug use.
- Maintain stable caffeine consumption of  $\leq 400$  mg per day.
- Avoid alcohol use. (Although subjects will be encouraged to avoid alcohol entirely, acceptable use is  $\leq 14$  drinks per week or  $< 5$  drinks on any day for men, and  $\leq 7$  drinks per week or  $< 4$  drinks on any day for women.)
- Avoid the consumption of grapefruit or grapefruit juice.
- Avoid travelling > 3 time zones.
- Avoid naps.
- Avoid starting new medications unless they become necessary in the opinion of a physician.
- Use an acceptable form of birth control.

Subjects will maintain daily sleep diaries during the sleep/wake monitoring period which will capture the following data points: lights out and wake clock times, estimated sleep latency, wake time in minutes after sleep onset, rating of sleep quality on a scale of 1-100, caffeine use, and atypical events.

#### **Day 8 (CCRC Admission)**

Subjects will enter the CCRC in the evening and a urine toxicology screen will be performed. A urine pregnancy test will be performed for female subjects of childbearing potential. Whether female subjects are in the follicular phase of their menstrual cycles will also be assessed at the time of admission. All subjects will be asked to report concomitant medications and AEs dating back to informed consent. Sleep diary data will

be reviewed to determine compliance with the required sleep/wake regimen. Compliance with other study-related instructions will also be assessed at this time. While at the CCRC, subjects will receive a prescribed lights out time which will be consistent with the lights out regimen that was followed during the baseline week. All subjects will be prescribed a 0700hr wake time during their stay at the CCRC.

Subjects will continue to maintain a daily sleep diary and wear an actigraph during their stay at the CCRC. Additionally, during each night at the CCRC, subjects will have their sleep monitored with ambulatory PSG. Subjects will also be screened for obstructive sleep apnea which will involve thermistor measurements, pulse oximetry for detection of oxygen desaturation events, and two channels of respiratory inductive plethysmography to measure chest and abdominal movement during breathing. Subjects with an apnea/hypopnea index  $\geq 10$  will be excluded from the data analysis.

#### **Day 9**

Subjects will be awakened at 0700 hrs and will remain in the CCRC for monitoring. Caffeine consumption should remain consistent with what the subject consumed throughout the sleep/wake monitoring period, and caffeine will not be allowed after 1330 hrs. Naps will be prohibited. During the evening (prior to lights out), AEs and concomitant medications will be assessed. Subjects will have their sleep monitored with PSG.

#### **Day 10 (Pre-Dose; 0700hrs – 1500hrs)**

Subjects will be awakened at 0700 hrs. Caffeine consumption will remain consistent with what the subject consumed throughout the sleep/wake monitoring period, and caffeine will not be allowed after 1330 hrs. Beginning at 1000 hrs, subjects will be administered a series of baseline (pre-dose) neurocognitive assessments, objective alertness assessments, and subjective assessments. All assessments will be administered by qualified, trained, research technicians. Assessments to be administered are described below:

Stanford Sleepiness Scale: Subjects will be asked to rate themselves along a 7-point scale ranging from 1 (fully alert) to 7 (extremely sleepy). This scale will be administered just prior to each administration of the MWT. Administration time is less than 5 minutes.

Maintenance of Wakefulness Test: Subjects will be placed in a dimly lit room where they will sit comfortably and receive instruction to keep their eyes open and attempt to remain awake while being monitored via standard MWT EEG leads. If the subject falls asleep, he/she will be awakened after three epochs of sleep as determined by EEG trace. Administration time is 20 minutes.

Psychomotor Vigilance Test: Subjects will be required to press a button each time a target is presented. Administration time is 10 minutes.

Rey Auditory Verbal Learning Test – List 1: Each subject will be read a list of 15 words and asked to repeat back as many as they can remember. The task is repeated 4 more times. Subsequently, a new interference list is read and the subject is asked to repeat back items from that list. Then the subject is asked to recall items from the original list. Administration time is approximately 10 minutes.

Continuous Performance Test II: Subjects will be required to press the space bar or click the mouse button when any letter except for the target letter “X” appears. Administration time is 15 minutes.

Symptom Checklist: Subjects will be asked if they are experiencing specific symptoms commonly associated with hypnotics. If they endorse any of the symptoms on the checklist, they will be asked whether the symptoms are mild, moderate, or severe. Administration time is approximately 5 minutes.

Vital signs (sitting blood pressure and heart rate) will be obtained several times throughout Day 10. Staff will also query for AEs at these time points.

## 6.2 Study Dosing

### Day 10 (Dosing and Post-Dose, 1500hrs - 2200hrs)

Subjects will dose at 1500 hrs. Shortly after dosing, a PVT administration will take place. MWTs (preceded by the SSS each time) will be administered at 1530 hrs, 1730 hrs, 1930 hrs, and 2130 hrs.

Based on the literature (3), it is estimated that almorexant will reach peak blood concentration between 1600 hrs and 1800 hrs. Around this timeframe, subjects will be administered the PVT, CPT, and SC, in addition to the MWT and SSS. The following neurocognitive assessments will also be administered during this timeframe:

Paired-Associates Learning Task: Subjects will be read 10 pairs of words. They will then be read, in a different order, the first word from each pair for which they are to recall the associated second word. The list will be presented and followed by recall two more times (with pairs in a different order each time). The first administration of the Paired-Associates Learning Task (given during the timeframe of 1600hrs – 1800hrs) will test immediate recall, during which errors are corrected. The test will be administered again several hours after the first administration using the same word list to assess delayed recall. Errors will not be corrected during the delayed recall trial.

Rey Auditory Verbal Learning Test – List 2: The RAVLT will be administered again during the 1600 – 1800hrs timeframe, but with a new list.

Grooved Pegboard Test: The test consists of 25 holes with randomly positioned slots. Pegs with a key along one side must be rotated to match the hole before they can be

inserted and subjects must place the pegs in the holes as quickly as possible. Administration time is approximately 10 minutes.

Stroop Color-Word Test: Subjects will be given three sheets of paper, one at a time. The Word page consists of the words “red,” “green,” and “blue” printed randomly in rows in black ink. Subjects will be asked to read as many words as they can out loud in a 45 second time period. The Color page consists of 100 items, all written as “XXXX,” printed in either green, red, or blue ink. Subjects will be asked to name as many colors as they can out loud in a 45 second time period. The Color-Word page consists of the words from the Word page printed in the colors from the Color page. The words and the colors they are printed in do not match one another. Subjects will be asked to name as many colors as they can in a 45 second time period. Total administration time is approximately 10 minutes.

Tower Test from Delis-Kaplan Executive Function System: Subjects will be asked to complete problem-solving tasks which will involve moving disks on pegs to match an arrangement shown to them in a picture. Administration time is approximately 20 minutes.

Digit Span: Subjects will be read a sequence of digits and asked to repeat the digits in the same sequence. For the second portion of the test, subjects will be read a sequence of digits and asked to repeat the digits in reverse order. For the third portion of the test, subjects will be read a sequence of digits and asked to repeat the digits in order from the lowest number to the highest. Administration time is approximately 6 minutes.

After the time window of 1600 hrs - 1800 hrs, subjects will receive additional administrations of the PVT, SC, and RAVLT (third list). Two more MWT administrations will also take place. The final assessment will begin at 2130 hrs.

Study personnel will remain with the subjects throughout testing and subjects will be kept awake until all assessments have been completed. Some of the neurocognitive tests will be audio recorded for quality control purposes.

#### **Night 10 (Post-Dose)**

AEs will be assessed prior to the prescribed lights out time. Subjects will engage in undisturbed, PSG recorded sleep.

#### **Day 11 (Discharge)**

Upon awakening at 0700 hrs, subjects will have all electrodes removed and will be debriefed prior to being discharged from the CCRC. AEs will be assessed prior to discharge.

### **Safety Follow-Up**

Within 5 – 12 days of dosing with study drug, subjects will be required to have a blood draw performed for a liver function test. This procedure will be performed at the SFDVAMC. Approximately 5ccs of blood will be drawn and analyzed at the SFDVAMC laboratory. If lab values are out of range, the subject may be asked to repeat the blood draw for a retest. The occurrence of AEs and concomitant medications since the day of discharge will be assessed.

## **7. STUDY OUTCOMES AND SAFETY ASSESSMENTS**

### **7.1 Study Outcome Assessment Measures**

A description of the measures which will be utilized for the outcome analyses is provided below:

Psychomotor Vigilance Test: The PVT is a widely used instrument that measures sustained attention and reaction time (49). Extensive work with this measure has demonstrated that the PVT is not affected by practice effects and is a highly sensitive measure of the effects of disrupted circadian rhythms from shift work (17) and chronic sleep deprivation (18, 19). PVT-192® devices will be utilized for this study. The PVT has a random inter-stimulus interval of 2-10 seconds and can be collected over a 10 minute period. The main measure will be performance lapses (reaction time > 500 ms) per 10 minute period. Secondary measures will include total time of lapses, frequency of false responses, frequency of non-responses, durations of the 10% fastest and 10% slowest responses, and performance decrement across time on the task.

Stanford Sleepiness Scale: The SSS is a subjective measure of sleepiness in which subjects rate themselves along a 7-point scale ranging from 1 (fully alert) to 7 (extremely sleepy) (50). Subjective sleepiness ratings will be collected in order to verify the sedative effects of zolpidem and the two doses of almorexant.

Maintenance of Wakefulness Test: The MWT is widely used to demonstrate significant pre and post treatment differences in excessive sleepiness. Sleep onset is defined as the first occurrence of > 15 seconds of cumulative sleep in a 30 second epoch. Latency to the first 30 seconds of sleep will be scored online by the attending sleep technologist. The subject will be awakened within 90 seconds of falling asleep.

Rey Auditory Verbal Learning Test: The RAVLT is a word learning task and a measure of short-term auditory memory and learning, as well as delayed auditory memory (52, 53).

Grooved Pegboard Test: A measure of manipulative dexterity, this test requires complex visual-motor coordination (51).

Paired-Associates Learning Task: This associative learning sub-test of the Wechsler Memory Scale tests the ability to learn and recall pairs of words, some of which are related (e.g., north/south) and others which are unrelated (e.g., eagle/jury) (47). Immediate and delayed recall trials will be scored for the number of correctly recalled pairs.

Continuous Performance Test II: The CPT assesses attention and working memory as well as executive function (44). Specifically, the CPT measures response inhibition via commissions (an aspect of executive function) and sustained attention via omissions. There is evidence in the literature which suggests that continuous performance tasks are sensitive to sleep-inducing agents (34). Scores will be based on response time and errors, inclusive of omissions and commissions.

Stroop Color-Word Test: The Stroop is a widely used putative measure of executive function that measures response inhibition (35). The Color-Word score will be computed, which measures the subject's ability to inhibit or override the tendency to produce the more automatic or dominant response (i.e., to name the color word rather than the color).

Tower Test from Delis-Kaplan Executive Function System: D-KEFS Tower is typically used for the assessment of executive function, specifically to detect deficits in planning, decision making, and problem solving (45). Literature provides evidence of a link between performance on towers tasks and sleep (32).

Digit Span: Digit Span is a subtest of the WAIS-IV which measures attention and working memory and has been found to be sensitive to sleep-inducing agents (36, 48).

The following measures will serve as covariates:

Actigraphy: The primary actigraph measures are habitual sleep onset and offset times and the range of variability around these data points. The wrist actigraph provides continuous activity data using a battery-operated wristwatch-sized microprocessor that senses motion with an accelerometer. Subjects can also indicate lights on, lights off, and other salient events by pressing an event marker on the actigraphs. The actigraphs will be initialized with the ActMe program (Ambulatory Monitoring, Inc.) using the PIM sampling mode in one-minute epochs for conventional actigraphic sleep-wake estimation.

Polysomnography: The primary PSG measure is total sleep time on the night prior to the day of dosing and neurocognitive testing. PSG recordings will be obtained with ambulatory PSG and the parameters recorded will follow current guidelines as defined in the AASM Manual for the Scoring of Sleep and Associated Events (37).

The Embla Titanium ambulatory recorders record up to 34 channels. The sampling frequency ranges from 256Hz to 512 Hz. High and low frequency filters will be added while scoring the data manually and in spectral analysis. 60Hz notch filters may be applied to remove electrical noise. Raw files will be kept with only anti-aliasing filters.

Spectral analysis will organize sleep epochs by stage and time. Artifacts will be tagged for removal for spectral analysis.

## 7.2 Safety Assessment Measures

Symptom Checklist: This checklist captures common symptoms experienced by subjects taking hypnotic medications. Reports of symptoms will be collected in order to compare possible drug side effects.

AEs will be assessed on a regular basis throughout the study and at the follow-up visit.

A liver function test will be performed on all subjects within 5 – 12 days of dosing with study drug.

## 8. ADVERSE EVENT REPORTING

### 8.1 Adverse Event Definitions

An AE is defined as any untoward medical occurrence that takes place in a clinical study, regardless of the causal relationship of the event with the investigational drug or study treatment(s). Any event occurring after the clinical trial participant has signed the study informed consent documentation should be recorded and reported as an AE.

An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to the investigational product. A new condition or the worsening of a pre-existing condition will be considered an AE.

An abnormal test finding will be classified as an AE if one or more of the following criteria are met: a.) the test finding is accompanied by clinical symptoms; b.) the test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention, including significant additional concomitant drug or other therapy; c.) the test finding leads to discontinuation of subject participation in the clinical study; d.) the test finding is considered an AE by the Investigator-Sponsor of the IND application.

For each AE, the date and time of onset, a description of the event, severity, seriousness, action taken, relationship to the study drug, outcome, and date of resolution will be recorded.

A **Serious Adverse Event (SAE)** is defined as an AE that results in any of the following:

- Death
- Life-threatening event – An event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires hospitalization or prolongs existing inpatient hospitalization, not inclusive of a pre-planned elective hospital admission for treatment of a pre-existing condition that has not significantly worsened or a diagnostic procedure.
- Results in persistent or significant disability or incapacity.
- Results in congenital abnormality or birth defect.
- An important medical event occurs which requires medical intervention to prevent any of the above outcomes. Important medical events are those which may not be immediately life-threatening but may jeopardize the subject and may require intervention to prevent one of the serious outcomes listed above.

An **Unexpected Adverse Event** is defined as any AE in which the frequency, specificity, or severity is not consistent with the risk information described in the clinical protocol or elsewhere in the current IND application or Investigator's Brochure.

## **8.2 Recording Requirements**

### *8.2.1 Eliciting Adverse Event Information*

AEs will be assessed when subjects check into the CCRC and again during each evening at the CCRC. Additionally, subjects will complete a Symptom Checklist at various scheduled time points throughout the day of dosing and asked to report the occurrence of any other AEs.

### *8.2.2 Recording Requirements*

All observed or volunteered adverse drug events (serious or non-serious) and abnormal test findings, regardless of treatment group or suspected causal relationship to the investigational drug or study treatment(s) will be recorded in the subjects' case histories. For all AEs, sufficient information will be pursued and/or obtained so as to permit a.) an adequate determination of the outcome of the event; and b.) an assessment of the causal relationship between the AE and the study drug.

AEs or abnormal test findings felt to be associated with the investigational drug or study treatment(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Investigator-Sponsor.

## **8.3 Reporting of Adverse Events**

### *8.3.1 Reporting of Adverse Events to the FDA*

#### *Written IND Safety Reports*

The Investigator-Sponsor will submit a written IND Safety Report to the responsible new drug review division of the FDA for any observed or volunteered AE that is determined

to be a.) associated with the investigational drug or study treatment(s); b.) serious; and c.) unexpected. Each IND Safety Report will be prominently labeled, "IND Safety Report."

Written IND Safety Reports will be submitted to the FDA as soon as possible and within 15 calendar days following the Investigator-Sponsor's receipt of the respective AE information. For each written IND Safety Report, the Investigator-Sponsor will identify all previously submitted IND Safety Reports that addressed a similar AE experience and will provide an analysis of the significance of newly reported AE in light of the previous, similar report(s).

Follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the relevant information is available. If the results of the Investigator-Sponsor's follow-up investigation show that an AE that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Investigator-Sponsor will submit a written IND Safety Report as soon as possible and within 15 calendar days after the determination was made.

In accordance with FDA requirements, annual safety reports will be submitted to the FDA.

#### *Telephoned IND Safety Reports*

In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Investigator-Sponsor will notify the responsible review division of the FDA by telephone or facsimile transmission of any observed or volunteered AE that is a.) associated with the use of the investigational drug or study treatment(s); b.) fatal or life-threatening; and c.) unexpected.

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Investigator-Sponsor's initial receipt of the respective human AE information.

#### *8.3.2 Reporting Adverse Events to the Responsible IRBs*

In accordance with applicable IRB policies of the Veterans Affairs Medical Center Research and Development Committee, University of California, San Francisco Committee on Human Research, and the U.S. Army Medical Research and Materiel Command Human Research Protection Office (USAMRMC HRPO), the Investigator-Sponsor will report, to the IRBs, any observed or volunteered AE that is determined to be associated with the investigational drug or study treatment(s), serious, and unexpected. AE reports will be submitted to the IRBs in accordance with the respective IRB procedures.

Applicable AEs will be reported to the IRBs as soon as possible and, in no event, later than 10 calendar days following the Investigator-Sponsor's receipt of the respective information. Follow-up information to reported AEs will be submitted to the IRB as soon

as the relevant information is available. If the results of the Investigator-Sponsor's follow-up investigation show that an AE that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting, the Investigator-Sponsor will report the AE to the IRB as soon as possible, but in no event later than 10 calendar days after the determination was made.

In accordance with the USAMRMC HRPO requirements, unanticipated problems involving risk to volunteers or others, serious adverse events related to participation in the study and all subject deaths related to participation in the study should be promptly reported by phone (310-619-2165), by e-mail ([hsrrb@amedd.army.mil](mailto:hsrrb@amedd.army.mil)), or by facsimile (301-619-7803) to the USAMRMC HRPO. A complete written report should follow the initial notification. In addition to the methods above, the complete report can be sent to the USAMRMC, ATTN: MCMR-ZB-P, 504 Scott Street, Fort Detrick, Maryland, 21702-5012.

The Medical Monitor is required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event to the USAMRMC HRPO. At a minimum, the Medical Monitor should comment on the outcomes of the event or problem and in the case of a serious adverse event or death, comment on the relationship to participation in the study. The Medical Monitor should also indicate whether he/she concurs with the details of the report provided by the Investigator-Sponsor. Reports for events determined by either the Investigator-Sponsor or Medical Monitor to be possibly or definitely related to participation and reports of events resulting in death will be promptly forwarded to the HRPO.

#### *8.3.3 Reporting of Adverse Events to Actelion Pharmaceuticals*

Copies of all periodic safety reports (including draft versions for review) to be submitted to the FDA will be provided to Actelion at least 10 days prior to their submission to the FDA. Copies of any MedWatch forms submitted to the FDA will be provided to Actelion immediately upon submission to the FDA.

All serious adverse events, regardless of causality and expectedness, will be reported to Actelion within 24 hours of the Investigator-Sponsor's knowledge of the event.

#### *8.3.4 Withdrawal of Subjects Due to Adverse Events*

Withdrawal of subjects due to an AE can take place at any time during the study at the discretion of the Investigator-Sponsor. Subjects may also choose to discontinue participation at any time.

## **9. STATISTICAL METHODS/DATA ANALYSIS**

### **9.1 Study Endpoints**

### 9.1.1 Analysis of Primary Endpoints

It is hypothesized that subjects receiving zolpidem 10mg will show greater impairment in neurocognitive performance and objective measures of sleepiness compared to subjects receiving placebo, almorexant 100mg, or almorexant 200mg. This hypothesis will be tested by comparing groups on post-medication performance tests using pre-medication test scores as covariates. When multiple administrations of a performance test are given either pre- or post-medication, mixed effects models will be used, with the group by time (pre- or post-medication) interaction effect serving as the test of the hypothesis. When a test is administered only once pre- and post-medication, the statistical test will be a one-way ANCOVA comparing mean scores on the four groups, with the pre-medication test score serving as the covariate. Covariates in all models will include total sleep time measured by PSG on the night before testing and average sleep duration measured by actigraphy. Planned comparisons will be conducted to compare the zolpidem 10mg group with placebo, almorexant 100mg, and almorexant 200mg separately. Post-hoc comparisons will be made to compare placebo vs. almorexant 100mg, placebo vs. almorexant 200mg, and almorexant 100mg vs. almorexant 200mg. For post-hoc comparisons, p-value adjustments will be made using a re-sampling procedure as implemented in the SAS “simulate” adjustment option.

Two-tailed significance tests will be conducted at the  $p = .05$  level. P-value adjustments will be made for multiple endpoint variables within each domain of neurocognitive functioning (verbal memory, attention/working memory, motor skills, executive function, and psychomotor vigilance) and objective sleepiness (sleep onset latency and low frequency EEG power in the MWT). The p-value adjustments will be made using a step-down, re-sampling based procedure (38, 39) which takes into account the correlational structure among the multiple variables. Primary analyses will be intent-to-treat analyses based on all participants randomized, regardless of dropout or missing data status. Dropout rate will itself be analyzed as a secondary outcome variable. Missing data will be carefully characterized, and multiple imputation will be used where necessary. The exact form of each mixed model, for example the correlational structure of repeated measures and whether heterogeneous group variances are included, will be made on the basis of best fit according to the Bayesian Information Criterion (BIC) before any hypothesis testing is conducted. Assumptions of the models (e.g., normal distributions of errors and absence of outliers) will be assessed, and any necessary remedies, such as data transformation or the use of robust standard errors, will be implemented before hypothesis tests are conducted.

Any deviations from the statistical plan will be described in the study manuscript.

### 9.1.2 Analysis of Secondary Endpoints

Secondary endpoints include sleep latency on the MWT measured beyond the presumed drug activity period at 270 and 390 minutes post-dose (i.e., the “hangover effect”), and subjective sleepiness measured by the Stanford Sleepiness Scale. Secondary analyses will

be conducted in a parallel fashion to the primary analyses, but with re-sampling based multiple comparison procedures for all significance tests.

## 9.2 Sample Size Determination

Enrollment is estimated to include up to 216 subjects to obtain 200 evaluable subjects. An equal number of subjects (up to 54) will be randomly assigned to each dosing group (almorexant 100 mg, almorexant 200 mg, zolpidem 10 mg, placebo). Randomization will be stratified on the basis of gender and caffeine use. With a power of 0.80 and an alpha of 0.05, the planned sample size will allow for the detection of effect sizes (Cohens'  $f$ ) of approximately 0.29. It is estimated that the effect of zolpidem 10 mg versus placebo on the cognitive performance measures will range from  $f = 0.34$  to  $f = 0.80$ , based on prior findings. Given the hypothesis that both doses of almorexant will be associated with significantly less impairment than zolpidem 10mg, it is possible that a range of effect sizes might be found with almorexant. If almorexant is absolutely no different than placebo, the study will be slightly overpowered to demonstrate its superiority over zolpidem. However, if almorexant has a more subtle impairment effect on cognition, intermediate between that seen with zolpidem 10 mg and placebo, it might become necessary to be able to detect somewhat smaller effects. According to guidelines suggested by Cohen (33), an effect size of  $f = .14$  is considered "small" and  $f = .39$  is considered "medium." Thus, the proposed study is well powered to test its main hypotheses.

## 9.3 Definition of Analysis Populations

Primary analyses will be intent-to-treat analyses based on all participants randomized, regardless of dropout or missing data status. If there are a substantial number of participant dropouts, separate analyses on completers only will be conducted as a sensitivity analysis, but hypothesis tests will be based on the intent-to-treat sample. No subgroup analyses are planned.

## 9.4 Safety Analysis

Dosing groups will be compared on each symptom included as part of the Symptom Checklist using Fisher's exact tests or Chi-Square approximations, depending on the frequency of each symptom. No p-value adjustments will be made.

## 10. QUALITY CONTROL (QC) AND QUALITY ASSURANCE

The study will be carried out according to requirements of the FDA and all other applicable agencies in addition to ICH accepted standards of GCP. All study-specific procedures will be performed according to approved written Standard Operating Procedures. Study monitors will be responsible for ensuring adherence to FDA and ICH guidelines. Study Monitors for this study will be provided by an external contract monitoring group. Regular monitoring of study data and files at the clinical study sites will be performed as defined in the study-specific monitoring plan. Additionally, an

authorized representative from the Investigator-Sponsor study team will perform an annual review of study files and training files to ensure adherence to GCP guidelines and study-specific standard operating procedures. Data collected during the study will be subjected to a thorough quality control review by the lead data managers prior to the statistical analysis. Specific requirements related to the data management QC of the study data will be detailed in the Data Management Plan. AE data will be reviewed on an ongoing basis with the Investigator-Sponsor.

## **11. DATA HANDLING, RECORD KEEPING, AND CONFIDENTIALITY**

### **11.1 Data Recording/Case Report Forms (CRFs)**

A CRF will be completed for each subject enrolled into the clinical study. The Investigator-Sponsor will review each completed CRF book and will complete the Investigator Statement. Completion of the Investigator Statement CRF confirms the Investigator-Sponsor's responsibility for ensuring that all data and corrections on the CRF are complete, accurate, and authentic.

Source documents will consist of laboratory and medical history records, screening instruments, actigraphy data, sleep diaries, PSG data, neurocognitive assessments, and subjective symptom measures including the Symptom Checklist, the Stanford Sleepiness Scale, and AE and concomitant medication disclosures. All necessary information from the source documents will be recorded on the CRFs. Where appropriate, certain data files will be merged with the study database electronically. Data recorded on the CRFs will be identical to the data recorded on the source documents. Queries will be issued to address all discrepancies noted within the study data. Any changes made to the study data as the result of a resolved query will be documented in the audit trail within the study database. Specific procedures related to the handling of blank, discrepant, or otherwise spurious data will be detailed in the Data Management Plan. When all data have been entered, validated and queries resolved, the database will be locked.

### **11.2 Record Maintenance and Retention**

The Investigator-Sponsor will maintain records in accordance with GCP guidelines and all applicable regulations and policies, to include:

- FDA correspondence related to the IND and clinical protocol, including copies of submitted Safety Reports and Annual Reports
- IRB correspondence (including approval notifications) related to the clinical protocol, including copies of AE reports and annual or interim reports
- Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s) and, if applicable, subject recruitment advertisements
- Signed FDA Form 1572 Statements of Investigator
- Financial disclosure information

- Curriculum vitae for the Investigator-Sponsor and all clinical protocol sub-investigators and study personnel
- Certificates of required training for Investigator-Sponsor, all sub-investigators, and other relevant study team members
- Listing of printed names/signatures of Investigator-Sponsor and listed sub-investigators
- Normal values for laboratory ranges
- Laboratory certification information
- Instructions for on-site preparation and handling of the investigational drug, other study treatments, and study materials
- Standard procedures for decoding and breaking the study blind
- Master randomization list
- Signed informed consent forms
- Completed Case Report Forms, signed and dated by the Investigator-Sponsor
- Source Documents
- Monitoring visit reports
- Copies of Investigator-Sponsor correspondence to sub-investigators, including notifications of safety information
- Subject screening and enrollment logs (a listing of all volunteers who signed informed consent)
- Subject identification code list
- Investigational drug dispensing and accountability records, including documentation of drug disposal
- Final clinical study report

The Investigator-Sponsor will retain the specified records and reports for a minimum of two years after the marketing application is approved for the investigational drug. If a marketing application is not submitted or approved for the investigational drug, records will be retained until 2 years after investigations under the IND have been discontinued and the FDA so notified.

### 11.3 Confidentiality

Participation in research will involve a loss of privacy, but information about subjects will be handled as confidentially as possible. Medical records will be created at UCSF and SFVAMC because of subjects' participation in this study. Information related to informed consent and screening test results will be included in the medical records, as well as information pertaining to vital signs, adverse events, and concomitant medications assessed during the hospital portion of the study. Therefore, other doctors may become aware of the individual's study participation. Hospital regulations require that all health care providers treat information in medical records confidentially. At the time of consent, subjects will be asked to sign forms to authorize the release of their personal health information for research purposes.

If it is suspected that the subject is in danger of harming him/herself or someone else, or if child abuse or neglect or elder abuse has occurred, appropriate authorities will be notified as required by law. It is also possible that subjects' research records could be subpoenaed by a court.

If information from this study is published or presented at scientific meetings, subjects' names and other personal information will not be used.

All study data will all be coded with a code number unique to the study. Only study personnel, with the permission of the Investigator-Sponsor, will have access to the key with the name and ID codes. The subject identification code list will be stored electronically in a password-protected, restricted access folder on a secured study server in order to maintain confidentiality. The only individuals receiving access to the code list will be the team member responsible for maintaining the list and a back-up.

The clinical interviews performed at screening will be audio recorded and will be used only by research personnel in order to calibrate the clinicians' ratings on the standardized interview format. The neurocognitive assessments performed on Day 10 will also be recorded for QC and calibration purposes. All recordings will be labeled with a unique code number and retained in a secure location (digital recordings will be encrypted, passcode protected, and stored and accessed via the secure VA server). Recordings will be retained until the conclusion of the study; at that point, they will be erased. Subjects will be informed that their screening clinical interviews will be audio recorded for the purpose of allowing the research team to ensure consistency across all clinical interviews. They will be informed that the recordings will be maintained under secure conditions at all times and identified only by the unique Subject ID number. Subjects will also be informed that the recordings will be deleted after the conclusion of the study.

The Maintenance of Wakefulness Tests performed on Day 10 will be video recorded and will be used only by research personnel for the purpose of confirming subjects' ability to remain awake during the testing process. The recordings will be labeled with a unique code number and retained in a secure location (digital recordings will be encrypted, passcode protected, and stored and accessed via the secure VA server). Recordings will be retained until the conclusion of the study; at that point, they will be erased. Subjects will be informed that their Maintenance of Wakefulness Tests on Day 10 will be video recorded for the purpose of allowing the research team to confirm their ability to remain awake during testing. They will be informed that the recordings will be maintained under secure conditions at all times and identified only by the unique Subject ID number. Subjects will also be informed that the recordings will be deleted after the conclusion of the study.

Organizations that may look at and/or copy subjects' medical records for research, quality assurance, and data analysis include representatives from the following:

- UCSF CHR
- FDA

- USAMRMC
- Actelion Pharmaceuticals, Ltd.

## **12. ETHICS**

### **12.1 Institutional Review Board (IRB) approval**

Prior to initiating the study, the Investigator-Sponsor will obtain approval in writing from all required IRBs. Specifically, approval must be obtained from the UCSF Committee on Human Research, the Veterans Affairs Research and Development Committee, and the U.S. Army Medical Research and Materiel Command Office of Research Protections Human Research Protection Office.

Any amendments to the protocol or changes to the informed consent document must be approved by all IRBs prior to the implementation of those changes. The only circumstance in which a modification to the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the Investigator-Sponsor will promptly notify the IRBs of the modification.

The IRBs will be promptly notified of any deviation to the protocol that may have an effect on the safety of the subjects and the integrity of the study. This notification will occur as soon as the deviation is identified. All deviations will also be reported in the continuing review report and final study report.

A copy of the approved continuing review report and the local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available.

In the event that the IRB requires, as a condition of approval, substantial changes to a clinical protocol submitted under an FDA-accepted IND application, or in the event of an Investigator-Sponsor's decision to modify the previously accepted clinical protocol, the Investigator-Sponsor will submit a protocol amendment (prior to the implementation of the changes) to the IND describing any change to the protocol that would significantly affect the safety of subjects, the scope of the investigation, or the scientific quality of the study.

Records of IRB approval and other related correspondence will be maintained in the regulatory files for the study and will be subject to periodic audits and reviews by study monitors. Periodic status reports will be submitted to the IRB as required, and AEs/serious AEs will be reported to each IRB per their specific reporting requirements.

## **12.2 Ethical and Scientific Conduct of the Clinical Study**

The clinical study will be conducted in accordance with the current IRB-approved clinical protocol, ICH Guidelines on GCP, and relevant policies, requirements, and regulations of the FDA, UCSF CHR, the VA R&D Committee, the USAMRMC ORP HRPO, and all other applicable state and federal agencies. All procedures described in this protocol will be performed according to approved written SOPs unless otherwise stated.

## **12.3 Subject Informed Consent**

The Investigator-Sponsor will make certain that an appropriate informed consent process is in place to ensure that potential research subjects are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. The Investigator-Sponsor, or a staff member designated by the Investigator-Sponsor, will obtain the written, signed informed consent of each subject prior to performing any study-specific procedures. The date and time that the subject signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented in the subject's case history. The Investigator-Sponsor will retain the original copy of the signed informed consent form and a copy will be provided to the subject.

The Investigator-Sponsor will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the Investigator-Sponsor will obtain the informed consent of enrolled subjects for continued participation in the clinical study.

## **13. EARLY DISCONTINUATION CRITERIA**

A subject may withdraw or be withdrawn from the study for the following reasons:

- 1.) Subject withdrew consent
- 2.) Investigator judgment
- 3.) Protocol violation(s)
- 4.) Non-compliance
- 5.) Adverse Event
- 6.) Pregnancy
- 7.) Other

If subjects withdraw consent prior to admission to the CCRC, they will be asked to return to the SFDVAMC for an early discontinuation visit which will entail an assessment of AEs and concomitant medications, a debriefing, and the return of study-related equipment.

If it becomes necessary to stop parts or all of the clinical study for the safety of the subjects, Actelion, the IRBs, and the FDA will be notified promptly of the discontinuation of the entire clinical study. Respective protocol modifications will be submitted prospectively to the IRB and to the FDA for discontinuation of parts of the clinical study. All sub-investigators will be notified of any necessary discontinuations.

Subjects participating in the study at the time of the discontinuation of a portion or all of the study will be promptly notified and advised of the impact of the discontinuation upon their study schedules. If a portion of the study is discontinued, subjects will be provided with revised informed consent documentation which will need to be signed prior to their continued enrollment in the study.

#### **14. RISKS AND BENEFITS**

Study-related risks and associated measures to minimize the risks are listed below:

##### **Study Drug Related Side Effects**

Some subjects might experience side effects associated with the study drugs. The list of possible side effects presented below is based on side effects that have been observed in clinical trials involving Almorexant and Zolpidem. Participants in these clinical studies took many different dosages of these drugs ranging from 1mg to 1000mg. Subjects will be told to discuss any side effects with study personnel as they occur. The nursing staff at the CCRC and study personnel will also closely monitor subjects on the day of dosing with study drug. All subjects will have a liver function test performed within 5 – 14 days of dosing with study drug.

##### **Risks and side effects related to taking Almorexant include those which are:**

###### Likely (occurring in greater than 20% of people)

- Drowsiness

###### Less Likely (occurring in less than or equal to 20% of people)

- Fatigue
- Headache
- Dizziness
- Nausea
- Liver Enzyme Elevations (mainly with administration for longer than two weeks of daily almorexant 100mg and 200mg)

###### Rare but Serious

- Heart rate abnormality (less than 1%)
- Convulsions (less than 1%)

##### **Risks and side effects related to taking Zolpidem include those which are:**

###### Less Likely (occurring in less than or equal to 20% of people)

- Dizziness
- Drowsiness

- Headache
- Diarrhea
- Fatigue

Rare but Serious

- Heart rate abnormality (less than 1%)
- Severe allergic reaction (less than 1%)

Also, in rare cases (.1% - 1%), people taking Zolpidem have reported engaging in unusual behaviors (e.g., driving, preparing and eating food, or making phone calls) while not being fully awake after taking Zolpidem, with no later memory of the events. However, these events occurred when people went to sleep after taking Zolpidem. During this study, subjects will remain awake and in a controlled, monitored setting after being given the study drug, so unusual behaviors are unlikely to occur.

Lastly, data has shown that small amounts of Zolpidem present in the blood up to 8 hours after taking the drug can harm performance in tasks involving full alertness, such as driving. This risk is most applicable to women, but could also apply to men. Because of this, the FDA has lowered the currently recommended dose of Zolpidem for women from 10mg to 5mg. If a subject is randomly assigned to take Zolpidem in this study, he/she will be given 10mg, which is twice the recommended dose for women. However, subjects will be given study drug at 3pm on Day 10 and will not be discharged until 8am the next day (17 hours after taking the sleep aid), so driving impairments are unlikely to occur.

**Blood Drawing (Venipuncture)**

The risks of drawing blood include temporary discomfort from the needle stick, bruising, and rarely, infection. The amount of blood collected to determine eligibility is approximately 20 ccs or 4 teaspoons. Only a qualified phlebotomist will draw blood following standard SFVAMC lab procedures.

**Clinical Interview & Questionnaires**

The interview and questionnaires may be distressing to some participants. Subjects will be told that they are free to decline to answer any questions or to stop the interviews at any time. The interviewer will be available to immediately assist with any problems that arise in the interview and will make a referral if required.

**Audio Recording – Clinical Interview and Neurocognitive Tests**

The clinical interviews and some of the neurocognitive tests will be audio taped. The audio taping may make subjects somewhat more uncomfortable than they would be without the taping. Research personnel will use the recordings in order to ensure that study staff are administering and scoring the tests correctly and in the same way. The audio recordings will be maintained under secured conditions (i.e., the recordings will be encrypted, protected with a pass code, and stored and accessed via a secure server), identified only by a unique ID number, and retained until the conclusion of the study, at which point they will be erased/deleted.

**Actigraphy**

There is no risk of injury from wearing the actigraph. Subjects might find it annoying to have to wear the actigraph 24 hours per day during the 10 day study. Subjects will be told that they can discuss any difficulties with this procedure with study personnel at any time. Subjects will also be able to decline to participate in this procedure at any time.

**Polysomnography**

There is no risk of injury from any of the recording devices, but subjects might experience slight discomfort from the attached electrodes and tape. High quality hypoallergenic materials will be used to minimize this risk.

**Video Recording – Maintenance of Wakefulness**

The Maintenance of Wakefulness Tests that will be conducted on Study Day 10 will be videotaped. The video recording may make subjects somewhat more uncomfortable than they would be without the taping. These recordings will only be reviewed by research staff and our consultants for the purpose of confirming subjects' ability to remain awake during the testing. The recordings will be identified by a unique ID number and will be stored under secure conditions (i.e., they will be encrypted, protected with a pass code and stored on a secure server). The recordings will be retained until the conclusion of the study, at which point they will be destroyed.

**Maintenance of Wakefulness Tests**

There is no risk of injury from taking this test, but subjects might find it annoying or difficult to remain awake while sitting quietly in a comfortable position. Subjects might also become bored while sitting still for the 20 minute duration of the test. Subjects will be able to stop the procedure at any time if they become uncomfortable.

**Neurocognitive Assessment Battery**

There is no risk of injury from completing the neurocognitive assessment battery, but subjects might become bored, frustrated, or find it difficult to concentrate as you take these tests throughout the day of testing. Subjects will be able to stop the procedures at any time if they become uncomfortable.

**Sleepiness**

There is a 3 out of 4 chance that subjects will take a sleep aid on Study Day 10 while at the hospital. Therefore, subjects might become sleepy during the study testing procedures, and the study staff will require subjects to remain awake. This might be difficult or frustrating for subjects.

**Reproductive Risks**

Subjects should not become pregnant or father a baby while participating in this study because the potential effects of the study drugs on an unborn baby are not known at this time. Women should not breastfeed a baby while on this study. Study staff will educate subjects regarding the importance of using appropriate birth control throughout the study.

**Unknown Risks**

The experimental drugs used in this study may have side effects or discomforts that no one knows about yet. Subjects will be told to discuss any side effects with study personnel as they occur. The nursing staff at the CCRC and study personnel will also closely monitor subjects on the day of dosing with study drug. Subjects will not experience any direct benefits by participating in the study. However, the study is contributing to medical knowledge related to the cognitive effects of sleep aids. Results could have implications for personnel of the military and/or other professions who have an occupational risk of poor sleep.

**15. STUDY PERSONNEL****15.1 Investigator-Sponsor**

The Investigator-Sponsor will assume overall scientific and administrative leadership for the study. He will be responsible for supervising the study team with regards to the recruitment, diagnostic assessment, and enrollment of subjects and the coordination of all study procedures.

The Investigator-Sponsor will have overall responsibility for the standardization of data collection, data quality control, data analysis, and interpretation. He will have overall responsibility for subject safety, rights, and welfare. He will be an active participant in the preparation of abstracts and manuscripts and will assure the dissemination of study findings in the professional and scientific communities.

**15.2 Medical Monitor**

The Medical Monitor may be asked to discuss research progress with the Investigator-Sponsor, consult on individual cases, or evaluate adverse event reports for the safety and protection of the subjects. The Medical Monitor shall promptly report discrepancies or problems to the IRB and the HRPO, and he will have the authority to stop a research study in progress, remove individual subjects from a study, and take whatever steps are necessary to protect the safety and well-being of research volunteers until the IRB can assess the Medical Monitor's report. At a minimum, the Medical Monitor will provide a written opinion regarding the relationship and outcome of any unanticipated problems related to participation, serious adverse events, and subject deaths.

**15.3 Co-Investigators**

The Co-Investigators assigned to this study will assist the research team in data collection, data analysis, quality control of study data, data interpretation, and the preparation of reports. They will provide consultation and oversight to the mental health clinicians and will assist with the determination of eligibility.

#### **15.4 Study Coordinator**

The study coordinator will be responsible for the day-to-day activities of the study, including but not limited to the following: obtaining informed consent, subject scheduling, eligibility determination, ensuring the completion of safety reports in a timely manner, case report form completion, ensuring that study team members are properly trained on study procedures, providing oversight to the external study monitors, and providing oversight for data completion, cleaning, analysis, and interpretation. The study coordinator will consult with the project director as necessary for high-level study management and budget oversight.

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